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Sleep Disturbances and Glucose Metabolism in Older Adults: The Cardiovascular Health Study

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OBJECTIVE

We examined the associations of symptoms of sleep-disordered breathing (SDB), which was defined as loud snoring, stopping breathing for a while during sleep, and daytime sleepiness, and insomnia with glucose metabolism and incident type 2 diabetes in older adults.

RESEARCH DESIGN AND METHODS

Between 1989 and 1993, the Cardiovascular Health Study recruited 5,888 participants ≥65 years of age from four U.S. communities. Participants reported SDB and insomnia symptoms yearly through 1989–1994. In 1989–1990, participants underwent an oral glucose tolerance test, from which insulin secretion and insulin sensitivity were estimated. Fasting glucose levels were measured in 1989–1990 and again in 1992–1993, 1994–1995, 1996–1997, and 1998–1999, and medication use was ascertained yearly. We determined the cross-sectional associations of sleep symptoms with fasting glucose levels, 2-h glucose levels, insulin sensitivity, and insulin secretion using generalized estimated equations and linear regression models. We determined the associations of updated and averaged sleep symptoms with incident diabetes in Cox proportional hazards models. We adjusted for sociodemographics, lifestyle factors, and medical history.

RESULTS

Observed apnea, snoring, and daytime sleepiness were associated with higher fasting glucose levels, higher 2-h glucose levels, lower insulin sensitivity, and higher insulin secretion. The risk of the development of type 2 diabetes was positively associated with observed apnea (hazard ratio [HR] 1.84 [95% CI 1.19–2.86]), snoring (HR 1.27 [95% CI 0.95–1.71]), and daytime sleepiness (HR 1.54 [95% CI 1.13–2.12]). In contrast, we did not find consistent associations between insomnia symptoms and glucose metabolism or incident type 2 diabetes.

CONCLUSIONS

Easily collected symptoms of SDB are strongly associated with insulin resistance and the incidence of type 2 diabetes in older adults. Monitoring glucose metabolism in such patients may prove useful in identifying candidates for lifestyle or pharmacological therapy. Further studies are needed to determine whether insomnia symptoms affect the risk of diabetes in younger adults.

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Sleep disorders are increasingly recognized as important factors in glucose metabolism and the development of type 2 diabetes. Sleep-disordered breathing (SDB), a condition characterized by a reduction or complete cessation of airflow during sleep, has repeatedly been linked to impaired glucose tolerance and insulin resistance in clinic-based studies (1,2) and, more recently, also in population-based studies (3). Another frequent sleep disorder, insomnia, which is defined as a subjective feeling of having difficulties initiating or maintaining sleep or having a feeling of nonrestorative sleep (4), has also been linked to impaired glucose metabolism (5,6).

Most previous work has used the HOMA of insulin resistance and sometimes the HOMA of β-cell function to estimate fasting insulin resistance and secretion, respectively (6,7). These methods are clearly limited in the setting of progressive insulin resistance and may be particularly limited in older adults, in whom peripheral insulin resistance is prevalent. Potentially better measures of insulin sensitivity and secretion can be derived from an oral glucose tolerance test (OGTT) (8,9). Little research has been done on sleep disorders and glucose metabolism using these potentially more refined measures of insulin sensitivity and secretion.

Recent data indicate that both SDB and insomnia symptoms are highly prevalent in patients with type 2 diabetes (10–12). Fewer studies have assessed the prospective association between these sleep disorders and the incidence of type 2 diabetes (13,14), and these have mainly focused on young or middle-aged adults.

Accordingly, we aimed to address several gaps in the literature, as follows: *1*) to focus on an elderly cohort in whom there are limited data on sleep disorders, glucose metabolism, and type 2 diabetes; *2*) to use longitudinal measures of glucose metabolism; and *3*) to consider symptoms of both SDB and insomnia, both of which are common in older populations.

RESEARCH DESIGN AND METHODS

Participant Recruitment

Between 1989 and 1990, a cohort of 5,201 participants was recruited from Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania. The cohort was identified using Medicare eligibility lists of the Health Care Finance Administration. Participants had to be ≥65 years of age, ambulatory and community dwelling, expected to remain in their communities for 3 years, and able to provide personal informed consent (15). In 1992–1993, an additional 687 predominantly African American participants were recruited, for a total of 5,888 participants.

Interviews and Clinical Examinations

Participants were contacted every 6 months, alternating between telephone interviews and visits to field centers, from 1989–1990 through 1998–1999. Sociodemographics (i.e., sex, age, race, marital status, and number of years of education completed), personal habits (i.e., smoking, alcohol consumption, and physical activity), and depressive symptoms were collected by questionnaires. Participants reported their usual frequency of consumption of beer, wine, and liquor, and the usual number of drinks consumed on each occasion, from which the number of drinks per week of alcoholic beverages was calculated. Physical activity (in kilocalories per week) was collected using a modified Minnesota Leisure-Time Activities questionnaire (16). Symptoms of depression were collected using the modified Center for Epidemiologic Studies Depression scale of 0–30 (17).

The participants were also asked about their medical history, and reported cardiovascular events (i.e., myocardial infarction and congestive heart failure [CHF]) were verified from objective information obtained from hospital and physician records, as previously described (18). Each year, participants reported whether they used over-the-counter sleeping pills at least weekly.

Study staff measured height, waist circumference, weight, and blood pressure at study examinations. BMI was calculated as weight (in kilograms) divided by height squared (in meters). Systolic blood pressure was measured twice, and the average of the two was used in the analyses. Cognitive impairment was assessed using the Digit Symbol Substitution Test (19). Medication use was assessed at baseline and annually from a validated medication inventory (20).

Sleep Symptoms

Participants were asked whether anyone had observed them having episodes where they stopped breathing for a while and then snorted or snored loudly, which we term "observed apnea." They were also asked whether their spouse or roommate had complained about their loud snoring, labeled "bothersome snoring," and whether they were usually sleepy in the daytime, labeled "daytime sleepiness."

In addition, the participants reported on the following three insomnia symptoms: whether they usually had difficulties falling asleep, labeled "sleep initiation problems"; experienced frequent nightly awakenings, labeled "sleep maintenance problems"; or usually woke up too early without being able to go back to sleep, labeled "early morning awakenings." The response options on all sleep questions were "yes," "no," and "I don't know." The participants were asked these questions annually from 1989–1990 to 1993–1994.

Within a subgroup of Cardiovascular Health Study (CHS) participants who attended the Sleep Heart Health Study (SHHS) (21), we validated the self-reported SDB symptoms in the CHS against the objectively measured sleep variables in the SHHS. We compared the median values of objectively measured SDB in the participants reporting to have SDB symptoms. In the subgroup of ~1,000 participants, we found higher obstructive apnea-hypopnea index values, defined as all desaturations of ≥4%, among those participants reporting observed apnea (8.7 desaturations/h) compared with those without observed apnea (7.2 desaturations/h, $P = 0.05$), and among those reporting bothersome snoring (8.8 desaturations/h) compared with those without bothersome snoring (4.8 desaturations/h, $P < 0.001$). We also found increasing obstructive apnea-hypopnea index values with increasing number of SDB symptoms. The participants reporting daytime sleepiness in the CHS had a higher Epworth sleepiness score in the SHHS compared with those without daytime sleepiness in the CHS (median 9 and 6, respectively; $P < 0.001$). The insomnia symptoms in the CHS were also compared with the objectively measured sleep latency (i.e., in minutes) and sleep efficiency, defined as

the percentage of time scored as sleep during the sleep period, in the SHHS. We found that participants with sleep initiation problems had longer sleep latency (18.8 min) than those who did not report such problems (16.8 min, $P = 0.14$) and that those reporting problems with sleep maintenance had lower sleep efficiency than those without such problems (79.1% and 83.3%, respectively; $P < 0.001$). Those participants with early morning awakenings had less time in bed (7 min, $P = 0.03$) and a shorter total sleep time (11 min, $P = 0.01$) than those without this symptom.

Glycemic Outcomes

An OGTT was performed in 1989–1990. The venipuncture was performed in the morning during the visit after an overnight fast, and serum glucose levels were measured (Kodak Ektachem 700 Analyzer; Eastman Kodak, Rochester, NY) (22). After the fasting venipuncture, 75 g of glucose was given orally to consenting nondiabetic participants. A second venipuncture was performed 2 h later to obtain a 2-h glucose value. Fasting serum glucose levels were measured again in 1992–1993, 1994–1995 (nonfasting), 1996–1997, and 1998–1999. Supplementary Fig. 1 shows the timeline for the collection of sleep symptoms and the glycemic outcomes.

We estimated insulin sensitivity using the Gutt index (Gutt et al. [8]), and insulin secretion using the Stumvoll index (Stumvoll et al. [9]).

Incident type 2 diabetes was defined as new use of insulin or a hypoglycemic agent, a fasting glucose level of $\geq$7.0 mmol/L, or a nonfasting glucose level of $\geq$11.1 mmol/L.

Statistical Analysis

For descriptive purposes, we provide the clinical characteristics of participants according to daytime sleepiness, which is a potential consequence of either SDB or insomnia. We calculated the Pearson Φ coefficient to assess the relationships between the dichotomous sleep variables. Missing data on baseline covariates were imputed using methods described previously (23).

Using linear regression, we analyzed the cross-sectional associations of sleep symptoms with 2-h glucose levels and measures of insulin sensitivity and insulin secretion in 3,007 participants with information on sleep symptoms and glucose measurements, and without prevalent diabetes or CHF, who were enrolled into the study in 1989–1990. For cross-sectional analyses of fasting glucose, we combined the 3,007 measurements from 1989–1990 with 2,378 measurements from 1992–1993 (providing repeated measurements in the original cohort and incorporating the added African American cohort). We fit generalized estimating equation models with an identity link function and unstructured within-group correlation. Since not all included participants attended both measurements, we had 5,385 observations from a total of 3,797 participants after excluding participants with missing sleep symptoms or glucose values, and those with prevalent diabetes or CHF. The participant selection process is illustrated in Supplementary Fig. 2.

We next used Cox proportional hazards models to examine the associations of sleep symptoms with the subsequent risk of incident type 2 diabetes, estimating hazard ratios (HRs) and 95% CIs. Of the 5,888 enrolled participants, 3,528 participants were free of diabetes and CHF at baseline and were included in the analyses (Supplementary Fig. 3). The subjects stopped contributing person-time to the analyses when they received a diagnosis of type 2 diabetes or at the time of the last attended visit. We used the exact marginal method to handle ties.

We allowed the sleep variables to vary yearly (i.e., to be time dependent) to examine current effects. In some participants, the SDB symptoms resolved, but we do not have information about why this was the case. To examine the difference in risk between current and chronic symptoms, we reran the analyses by calculating the cumulative average of previous values of the sleep variables (0 or 1) each year and updating them in the model. Because waist circumference is a particularly strong risk factor for type 2 diabetes (24), we also allowed waist circumference to change over time in the same manner. We replaced each missing value of the time-dependent variables by the last observed value of that variable. We restricted our follow-up to 1998–1999, as this was the last year that fasting glucose levels were measured.

First, we ran separate models for observed apnea, bothersome snoring, and daytime sleepiness. Since observed apnea and bothersome snoring are frequently used as markers for SDB (14) and daytime sleepiness is a potential SDB consequence, we assessed their joint associations by creating a cumulative variable coded "0" for no symptoms, "1" for having one symptom, and "2" for two or more symptoms. Too few participants reported all three symptoms ($n = 63$) to be categorized separately. We treated insomnia symptoms similarly, first analyzing them separately and then combining symptoms into a cumulative variable based on the number of symptoms reported. Since daytime sleepiness also is a consequence of insomnia, we included it in the combined variable.

We adjusted for covariates in two multivariable models. In the first model, we adjusted for age, sex, race, waist circumference, and clinic site (Model 1). In the second model, we further adjusted for marital status (never married, married, separated/divorced/widowed); education ($<$12 years, 12 years, and 13+ years); smoking (never smoker, previous smoker, current smoker); alcohol consumption ($<$1 drink, 1–6 drinks, and $\geq$7 drinks); BMI; physical activity; depressive symptoms score; cognitive function; systolic blood pressure; antihypertensive medication use; levels of creatinine, albumin, and total cholesterol; and previous myocardial infarction (Model 2). In the analysis of the insomnia symptoms, we also adjusted for observed apnea; adjustment for observed apnea in analyses of SDB symptoms did not meaningfully alter their association with diabetes.

Those individuals living alone may be less likely to report sleep apnea or snoring, and we therefore excluded those participants living alone in a sensitivity analysis. Because of the association between SDB and insomnia, we also excluded those participants with observed apnea in another sensitivity analysis. We also conducted several prespecified stratified analyses to assess whether the associations of the sleep disorders with glucose metabolism and incident type 2 diabetes were modified by other factors. We stratified by sex, age (dichotomized at age 75 years), BMI (dichotomized at 30 kg/m^2), waist circumference (dichotomized at 95 cm), and race. We tested for multiplicative interaction

across strata with relevant cross-product terms. Because sleep disorders are strongly associated with chronic diseases, we excluded those participants with prevalent heart disease.

To examine whether the use of sleep medications changed the association between the sleep symptoms and type 2 diabetes, recognizing that it may be a cause or a consequence of sleep symptoms, we adjusted for this in separate sensitivity analyses. We tested the proportionality of hazards using log-log curves and tests of interaction with time and found no violations. We conducted all statistical analyses using Stata 12 for Windows (Stata Corp., College Station, TX).

RESULTS

The characteristics of participants according to reported daytime sleepiness are presented in Table 1. Participants with daytime sleepiness tended to be older, heavier, less physically active, less educated, and more depressed, and to have higher blood pressure. They also had a higher prevalence of observed apnea, bothersome snoring, and all three insomnia symptoms. Supplementary Table 1 shows the correlations among the sleep variables.

Glucose Metabolism

None of the individual SDB symptoms were associated with fasting glucose in the cross-sectional analyses (Table 2). There was, however, a graded trend toward increased fasting glucose levels with an increasing number of SDB symptoms. Participants experiencing daytime sleepiness had higher 2-h glucose levels than participants without this symptom, and the 2-h glucose level was much higher with an increasing number of SDB symptoms.

Sleep initiation problems and sleep maintenance problems were associated with lower fasting glucose levels compared with those levels in participants who did not report these symptoms. The cumulative number of insomnia symptoms was also associated with lower fasting glucose levels in a linear fashion (P for trend = 0.003). However, we found no consistent association of any of these insomnia symptoms with 2-h glucose levels.

We then examined insulin sensitivity and secretion (Table 3). We found lower insulin sensitivity associated with each of the SDB symptoms, with an inverse graded relationship between the number of symptoms and insulin sensitivity. We found similar corresponding results with SDB symptoms and greater insulin secretion. We found no clear association between insomnia symptoms and insulin sensitivity or insulin secretion, except for an association of sleep maintenance problems with increased insulin secretion.

Incident Type 2 Diabetes

Among the 3,528 participants, type 2 diabetes developed in a total of 208 participants during a mean follow-up time of 5.1 years. Table 4 presents the adjusted HRs and 95% CIs for incident diabetes in relation to time-dependent symptoms of SDB and insomnia, and their cumulative average. Participants reporting observed apnea, bothersome snoring, or daytime sleepiness had increased risks of the development of type 2 diabetes during the follow-up compared with those who did not report these symptoms. The time-dependent observed apnea was more strongly associated with incident type 2 diabetes than the cumulative average observed apnea. The cumulative number of SDB symptoms was also associated with increased risk of incident type 2 diabetes.

We found no evidence of an association for any of the insomnia symptoms with incident type 2 diabetes.

Additional Analyses

Restricting the analysis to those participants not living alone and to those without observed apnea or heart disease did not change the results considerably (data not shown). We also did not find evidence of effect modification by age, sex, race, BMI, or waist circumference.

The association of the sleep variables with glucose metabolism and type 2 diabetes risk did not change after adjustment for the use of sleep medications. For example, in Model 2, among those participants having two or more SDB symptoms, the estimated 2-h glucose level was 0.39 mmol/L (95% CI 0.09–0.67) higher

Table 1—Characteristics of the participants according to daytime sleepiness (yes/no)

	Daytime sleepiness (N = 3,528)		
Variable	No (n = 2,993)	Yes (n = 535)	P value
Age (years)	72.1 (5.3)	73.6 (5.8)	<0.001
Waist circumference (cm)	92.7 (12.6)	94.7 (13.3)	<0.001
Systolic blood pressure (mmHg)	138.1 (19.7)	141.1 (20.8)	0.001
Physical activity (kcal/week)	1,963.4 (2,192.0)	1,476.8 (1,725.9)	<0.001
BMI (kg/m^2)	26.1 (4.3)	26.8 (5.0)	0.01
Depression score	4.0 (4.2)	6.2 (5.0)	<0.001
Creatinine (μmol/L)	92 (25)	96 (30)	0.001
Albumin (g/dL)	40.0 (2.9)	39.8 (2.9)	0.02
Total cholesterol (mmol/L)	5.6 (1.0)	5.5 (1.0)	0.24
Digit symbol substitution test score	38.3 (13.0)	33.3 (14.0)	<0.001
Fasting glucose (mmol/L)	5.5 (0.5)	5.6 (0.6)	0.14
Male sex (%)	58.7	54.0	0.04
White race (%)	89.0	85.4	0.05
Current smokers (%)	11.5	13.1	0.13
Married (%)	75.0	70.5	0.02
Observed apnea (%)	7.2	12.0	<0.001
Bothersome snoring (%)	21.8	33.1	<0.001
Sleep initiation problems (%)	19.2	31.0	<0.001
Sleep maintenance problems (%)	60.8	75.0	<0.001
Early morning awakenings (%)	27.8	49.4	<0.001
Heavy drinkers (%)	15.4	12.9	0.03
College graduate (%)	46.4	36.1	<0.001
Use of antihypertensive medications (%)	41.5	44.3	0.22
Prevalent myocardial infarction (%)	7.1	6.5	0.63

Data are reported as mean (SD), unless otherwise indicated.

Table 2—Differences in mean fasting glucose examinations in 1989 and 1993 and 2-h glucose levels from the 1989 examination according to symptoms of SDB and insomnia

	Fasting glucose (mmol/L) (*N* = 5,385)						2-h glucose (mmol/L) (*N* = 3,007)					
		Model 1			Model 2			Model 1			Model 2	
	n	B	95% CI	*P* value	B	95% CI	*P* value	*n*	B	95% CI	*P* value	B	95% CI	*P* value
Daytime sleepiness	801	0.03	0.00–0.07	0.07	0.03	−0.01 to 0.06	0.16	444	0.38	0.15–0.62	0.001	0.35	0.11–0.59	0.004
Observed apnea	402	0.03	−0.02 to 0.08	0.19	0.03	−0.02 to 0.08	0.18	242	0.08	−0.23 to 0.40	0.61	0.10	−0.21 to 0.41	0.53
Bothersome snoring	1,113	0.02	−0.01 to 0.05	0.20	0.03	−0.01 to 0.06	0.12	695	0.12	−0.09 to 0.32	0.26	0.17	−0.03 to 0.37	0.10
SDB symptoms														
1	1,310	0.00	−0.03 to 0.03	0.89	0.00	−0.03 to 0.03	0.86	761	0.16	−0.04 to 0.36	0.11	0.14	−0.05 to 0.34	0.16
2–3	467	0.06	0.01–0.11	0.01	0.06	0.02–0.11	0.008	287	0.30	0.01–0.71	0.05	0.35	0.06–0.64	0.02
Linear trend				0.05			0.06				0.02			0.01
Sleep initiation	1,099	−0.02	−0.06 to 0.01	0.21	−0.04	−0.07 to 0.00	0.03	634	0.01	−0.20 to 0.22	0.91	−0.07	−0.28 to 0.14	0.52
Sleep maintenance	3,311	−0.04	−0.06 to −0.01	0.009	−0.04	−0.07 to −0.02	0.001	1,897	−0.04	−0.21 to 0.14	0.67	−0.05	−0.28 to 0.07	0.26
Early morning	1,630	0.00	−0.03 to 0.03	0.91	−0.01	−0.04 to 0.02	0.47	930	0.09	−0.09 to 0.27	0.33	0.07	−0.12 to 0.25	0.47
Insomnia symptoms														
1	1,828	−0.03	−0.06 to −0.01	0.12	−0.03	−0.06 to 0.00	0.08	1,044	−0.22	−0.43 to 0.00	0.05	−0.21	−0.43 to 0.00	0.05
2	1,266	−0.02	−0.06 to 0.05	0.19	−0.04	−0.08 to 0.00	0.03	720	0.09	−0.14 to 0.33	0.44	0.05	−0.18 to 0.29	0.65
3	607	−0.04	−0.09 to 0.01	0.09	−0.07	−0.11 to −0.1	0.01	339	0.00	−0.30 to 0.30	0.99	−0.07	−0.38 to 0.24	0.66
4	150	−0.01	−0.09 to 0.08	0.90	−0.04	−0.12 to 0.04	0.352	95	0.24	−0.26 to 0.74	0.34	0.13	−0.37 to 0.64	0.61
Linear trend				0.17			0.013				0.21			0.58

SDB symptoms include daytime sleepiness, observed apnea, and bothersome snoring. Insomnia symptoms include sleep initiation problems, sleep maintenance problems, early morning awakenings, and daytime sleepiness. Model 1, adjusted for age, sex, race, waist circumference, and clinic site. Model 2, adjusted for age, sex, race, marital status, clinic site, education, systolic blood pressure, use of antihypertensive medications, physical activity, smoking, alcohol use, BMI, waist circumference, depression score, creatinine level, albumin level, cholesterol level, prevalent myocardial infarction, digit symbol substitution test results, and observed apnea (for the insomnia symptoms, daytime sleepiness and bothersome snoring).

than in those without any SDB symptoms, and the HR for incident type 2 diabetes was 1.93 (95% CI 1.29–2.87).

CONCLUSIONS

In this population of older adults who were free of type 2 diabetes at baseline, having observed apnea, bothersome snoring, and daytime sleepiness were associated with increased fasting glucose levels, increased 2-h glucose levels, decreased insulin sensitivity, and increased insulin secretion. Each symptom of SDB was associated with an increased risk of incident type 2 diabetes in a time-dependent manner. When we combined them in a cumulative manner that suggested the presence of a more severe SDB, the risk of incident type 2 diabetes increased with an increasing number of symptoms. For the insomnia symptoms, we did not find a consistent association with glucose metabolism or incident type 2 diabetes, except for a fasting glucose level, where experiencing frequent awakenings through the night was associated with a decreased fasting glucose level. Surprisingly, there was also an inverse linear association between the number of insomnia symptoms and fasting glucose level.

Similar to our findings, recent cross-sectional studies (7,25) have found SDB to be associated with glucose intolerance and insulin resistance. These studies have relied on HOMA of insulin resistance and HOMA of β-cell function derived from fasting glucose and insulin measurements, while we used the Gutt index and the Stumvoll index to account for both fasting and 2-h glucose measurements derived from an OGTT. The Gutt index has been reported (26) to be sensitive to changes in glucose metabolism in individuals with moderate-to-severe sleep apnea who were treated with continuous positive airway pressure.

Limited previous evidence of a prospective association between SDB symptoms and incident type 2 diabetes exists, and the studies have mainly been small and not always sufficiently powered to detect an association (27). Similar to our findings, a study (28) objectively measuring sleep apnea in >4,000 participants who were 40–69 years of age reported an HR for incident type 2 diabetes of 1.69 (95% CI 1.04–2.96) among those participants with moderate-to-severe nocturnal intermittent hypoxia. A large

observational study (14) reported a relative risk of 2.25 (95% CI 1.71–2.40) for regular snorers compared with nonsnorers in almost 70,000 women in the Nurses' Health Study cohort. This relative risk is slightly higher than that in our sample, which may reflect the additional adjustment for waist circumference in our study or indicate that the relative risk from snoring for the development of type 2 diabetes may be lower in older adults.

In accordance with our findings, a recent study (5) reported increased rates of impaired glucose tolerance in SDB patients, but not in insomnia patients. However, a recent meta-analysis (13) of 10 studies including >100,000 participants found increased risks of the development of type 2 diabetes of 1.57 (95% CI 1.25–1.97) and 1.84 (95% CI 1.39–2.43), respectively, for sleep initiation and sleep maintenance problems. The participants in our study were all ≥65 years of age, and, as the amount of sleep may decrease with age, even in subjects without daytime sleepiness (29), the causes and correlates of insomnia in the elderly may differ from those in younger populations, possibly explaining differences between study findings.

We observed differences in associations once specific insomnia symptoms were analyzed, with one analysis showing a negative association of fasting glucose levels with sleep maintenance symptoms. This finding, as well as prior research, points to the need to consider each aspect of insomnia separately, as the health implications of sleep onset, sleep maintenance, and early morning awakenings may differ.

Sleep disorders are not constant over a lifetime (30), and this is the first prospective study to account for this by allowing the sleep exposure to change in yearly increments during the follow-up. The effect of observed apnea when allowing it to change over the follow-up period appeared to be stronger compared with using the cumulative average, indicating that current or recent sleep disruption may be more important than previous/chronic symptoms in the development of type 2 diabetes. The apparently stronger association of the more recent exposure of observed apnea is a new finding and needs to be confirmed by further studies.

Table 3—Differences in mean indices of insulin sensitivity (Gutt index) and insulin secretion (Stumvoll index) from the 1989 examination according to symptoms of SDB and insomnia

		Insulin sensitivity (N = 3,007)						Insulin secretion					
		Model 1			Model 2			Model 1			Model 2		
	n	B	95% CI	P value	B	95% CI	P value	B	95% CI	P value	B	95% CI	P value
Daytime sleepiness	444	−2.95	−5.28 to −0.62	0.01	−2.452	−4.86 to −0.18	0.04	40.0	−16.5 to 96.6	0.17	25.1	−32.9 to 83.0	0.40
Observed apnea	242	−3.35	−6.4 to −0.24	0.03	−3.40	−6.44 to −0.37	0.03	82.1	7.0–157.2	0.03	75.8	1.3–150.3	0.05
Bothersome snoring	695	−2.03	−4.02 to −0.03	0.05	−2.51	−4.47 to −0.56	0.01	56.9	8.6–105.2	0.02	52.76	4.5–100.6	<0.001
SDB symptoms													
1	761	−1.72	−3.66 to 0.22	0.08	−1.45	−3.36 to 0.47	0.14	49.5	2.5–96.5	0.04	38.9	−8.1 to 85.9	0.10
2–3	287	−4.34	−7.26 to −1.43	0.004	−4.76	−7.63 to −1.89	0.001	95.9	25.3 to 166.5	0.008	83.2	12.7–153.6	0.02
Linear trend				0.002			0.001			0.002			0.01
Sleep initiation	634	−0.98	−3.03 to 1.09	0.36	−0.21	−2.32 to 1.89	0.84	42.9	−6.9 to 92.8	0.09	30.0	−21.6 to 81.6	0.26
Sleep maintenance	1,897	0.01	−1.70 to 1.72	0.99	0.72	−1.03 to 2.48	0.42	43.7	2.3–85.1	0.04	42.8	−0.2 to 85.8	0.05
Early morning	930	−1.13	−2.92 to 0.65	0.21	−0.92	−2.73 to 0.89	0.32	−2.9	−46.1 to 40.3	0.90	−14.0	−58.3 to 30.3	0.54
Insomnia symptoms													
1	1,044	1.42	−0.70 to 3.53	0.19	1.56	−0.52 to 3.64	0.29	37.8	−13.5 to 89.0	0.15	25.1	−26.1 to 76.1	0.34
2	720	−1.32	−3.64 to 0.99	0.26	−0.72	−3.05 to 1.60	0.77	49.9	−6.2 to 106.0	0.08	33.4	−23.7 to 90.5	0.25
3	339	−0.65	−3.58 to 2.28	0.66	0.21	−2.79 to 3.22	0.98	29.9	−41.1 to 100.9	0.41	6.3	−67.5 to 80.1	0.87
4	95	−2.85	−7.76 to 2.05	0.25	−1.36	−6.31 to 3.58	0.59	126.1	7.31–244.9	0.04	90.8	−30.6 to 212.3	0.14
Linear trend				0.11			0.47			0.05			0.29

SDB symptoms include daytime sleepiness, observed apnea, and bothersome snoring. Insomnia symptoms include sleep initiation problems, sleep maintenance problems, early morning awakenings, and daytime sleepiness. Model 1, adjusted for age, sex, race, waist circumference, and clinic site. Model 2, adjusted for age, sex, race, marital status, clinic site, education, systolic blood pressure, use of antihypertensive medications, physical activity, smoking, alcohol use, BMI, waist circumference, depression score, creatinine levels, albumin levels, cholesterol levels, prevalent myocardial infarction, digit symbol substitution test results, and observed apnea (for the insomnia symptoms, daytime sleepiness and bothersome snoring).

Table 4—Symptoms of SDB and insomnia and 10-year risk of incident type 2 diabetes

	Events/person-time (208/29,234)	Model 1			Model 2		
		HR	95% CI	*P* value	HR	95% CI	*P* value
Daytime sleepiness	56/5,016						
Time dependent		1.62	1.19–2.21	0.002	1.58	1.15–2.18	0.005
Cumulative average		1.63	1.09–2.42	0.02	1.56	1.03–2.36	0.04
Observed apnea	24/1,626						
Time dependent		1.98	1.28–3.05	0.002	1.86	1.20–2.88	0.006
Cumulative average		1.54	0.90–2.64	0.12	1.44	0.84–2.48	0.19
Bothersome snoring	88/10,307						
Time dependent		1.30	0.97–1.75	0.08	1.28	0.95–1.72	0.11
Cumulative average		1.36	0.96–1.93	0.09	1.33	0.93–1.90	0.12
SDB symptoms							
1	82/10,572	1.37	1.00–1.87	0.05	1.34	0.98–1.84	0.07
2–3	40/3,034	2.12	1.44–3.13	<0.001	2.00	1.35–2.98	0.001
Linear trend				<0.001			0.001
Sleep initiation problems	41/5,999						
Time dependent		1.05	0.74–1.49	0.79	0.99	0.69–1.43	0.96
Cumulative average		1.03	0.69–1.54	0.88	0.94	0.61–1.43	0.77
Sleep maintenance problems	133/18,838						
Time dependent		0.94	0.71–1.26	0.69	0.87	0.65–1.17	0.36
Cumulative average		0.92	0.66–1.28	0.61	0.84	0.60–1.18	0.33
Early morning awakenings	68/9,183						
Time dependent		1.06	0.79–1.41	0.71	0.99	0.73–1.34	0.95
Cumulative average		0.95	0.68–1.33	0.76	0.87	0.61–1.24	0.43
Insomnia symptoms							
1	79/10,240	1.18	0.83–1.69	0.36	1.14	0.80–0.64	0.48
2	49/6,899	1.07	0.72–1.60	0.73	0.95	0.62–1.43	0.79
3	22/3,238	1.13	0.68–1.88	0.63	0.98	0.57–1.67	0.94
4	4/903	0.71	0.25–1.98	0.51	0.57	0.20–1.62	0.29
Linear trend				0.95			0.42

SDB symptoms include daytime sleepiness, observed apnea, and bothersome snoring. Insomnia symptoms include sleep initiation problems, sleep maintenance problems, early morning awakenings, and daytime sleepiness. Model 1, adjusted for age, sex, race, waist circumference, and clinic site. Model 2, adjusted for age, sex, race, marital status, clinic site, education, systolic blood pressure, use of antihypertensive medications, physical activity, smoking, alcohol use, BMI, waist circumference, depression score, creatinine levels, albumin levels, cholesterol levels, prevalent myocardial infarction, digit symbol substitution test results, and observed apnea (for the insomnia symptoms, daytime sleepiness and bothersome snoring).

The mechanisms that underlie our findings are largely unknown, but some have been suggested. Sleep deprivation, caused by SDB or insomnia, has been shown to increase the activity of orexin neurons that may act as a link between SDB and the metabolic effects (31). Sleep deprivation can also cause increased sympathetic nervous activity, increasing the released levels of cortisol and catecholamines, leading to reduced insulin sensitivity and glucose tolerance (32,33). The corresponding increase in insulin secretion may lead to β-cell exhaustion and impaired secretory capacity over time, resulting in diabetes.

Limitations

Despite its clear strengths, which include the population-based design in a high-risk older population, the wide range of covariates, the OGTT-based measures of insulin sensitivity and secretion, and the repeated measures of multiple sleep symptoms, the study also has important limitations.

We used self-reported measures of sleep, which, while subjective, have the advantage of ready clinical applicability at low cost. The participants were asked whether anyone had observed them having episodes where they stopped breathing for a while and then snorted or snored loudly or complained about loud snoring. Participants living alone may not have this knowledge and may have reported "no" rather than the option offered of "I don't know." Although objective measures of SDB (i.e., polysomnography results) exist, subjectively reported breath cessation is among the best clinical predictors of sleep apnea (34), and self-reported snoring is a sensitive but less specific measure (35). In a sensitivity analysis, we restricted the analysis to those not living alone, and this changed our estimates minimally. However, objective polysomnography data available in a subset indicated that the symptoms analyzed discriminated between groups with and without SDB symptoms. Furthermore, because misclassification between these symptoms and sleep apnea is unlikely to be related to glucose or insulin levels, our results may underestimate the true associations of sleep apnea with hyperglycemia and insulin resistance. The difference in sleep latency between those reporting sleep initiation problems and those who did not was only 2 min, but, as insomnia is defined as a subjective feeling of having difficulties falling asleep, remaining asleep, or receiving restorative sleep lasting at least 1 month and causing daytime impairment (4); thus, such problems are not ideally evaluated by polysomnography (36).

Information about sleep duration was not available in CHS. SDB and insomnia are different conditions than short sleep duration (37), and people with insomnia symptoms could have normal or long durations of sleep (38). Also, some people with short sleep duration may not have insomnia symptoms or daytime sleepiness, as individuals vary substantially in the duration of sleep that is needed for restoration (39).

Observational studies inherently limit causal inference. Although we adjusted for several potential confounders in our multivariable analyses, we cannot exclude the possibility of uncontrolled confounding behind the observed associations. However, any remaining confounder that is potentially able to influence our results would need to be strongly associated with both sleep symptoms and glucose metabolism, and generally be unrelated to the factors included in our models. Several small interventional studies (26,40) suggest that sleep apnea therapy may improve insulin resistance, supporting a causal relationship between SDB and insulin resistance. Of note, these interventional studies have in general excluded older individuals.

Summary

In this population-based study of older adults, having observed apnea, bothersome snoring, and daytime sleepiness were associated with impaired glucose metabolism, insulin resistance, and risk of incident type 2 diabetes. For observed apnea, more recent exposure tended to be more strongly associated with subsequent risk of type 2 diabetes than chronic exposure. The associations persisted after adjustment for total and central adiposity, suggesting that SDB may impair glucose metabolism independent of body fat. In contrast to previous studies, we found no consistent association between the insomnia symptoms and glucose metabolism or incident type 2 diabetes. Further studies are needed to determine whether insomnia symptoms affect the risk of incident type 2 diabetes differently in older adults than in younger adults.

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